REMARKS

Upon entry of the foregoing amendment, claims 258-345 are pending in the application, with 258, 302, 334, and 340 being the independent claims. Claims 265, 267, 269-274, 277, 280-282, 287, 288, 290, 291, 293, 294, 301, 304, 305, 307, 308, 315, 319, 321, 323-328, 331, 333, 335-337, and 341-343 have been withdrawn by the Examiner. Claims 258 and 302 have been amended to merely correct obvious typographical errors. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 103

(A) Claims 258-264, 266, 268, 275, 276, 278, 279, 283-286, 289, 292, 295, 296, 302, 303, 306, 309, 310, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344, and 345 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Watts *et al.* (International Application No. WO 97/05903) in view of Heiber *et al.* (U.S. Patent No. 5,346,701), and optionally any one or more of Teng *et al.* (U.S. Patent No. 6,747,014), Garces *et al.* (U.S. Patent No. 5,736,161), and Bachynsky *et al.* (U.S. Patent No. 5,190,748). (Office Action, page 3). Applicants respectfully traverse this rejection.

The Examiner alleges that Watts *et al.* discloses a drug delivery composition for delivery through oral administration, comprising a drug and an absorption promoter, which can be sodium caprate. (Office Action, page 5). The Examiner further alleges that Watts *et al.* teaches the use of a single enhancer with insulin and capric acid and that the absorption promoter comprises a fatty acid or a salt thereof which can be used alone. (Office Action, page 5).

Applicants respectfully disagree. The Supreme Court has articulated that obviousness under § 103(a) is determined by an analysis of the following factors: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective

evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The obviousness or nonobviousness of the subject matter is to be determined based on these considerations however, secondary considerations such as commercial success, long-felt but unresolved needs and the failure of others can be utilized to determine the circumstances surrounding the origin of the invention. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1730 (2007). If such secondary considerations exist, they must be considered. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-1539 (Fed. Cir. 1983).

In *KSR*, the Supreme Court also made clear that predicable variations are likely obvious, but unpredictable variations are not:

> If a person of ordinary skill can implement a predicable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative - a court must ask whether the improvement is more than the predicable use of prior art elements according to their established functions.

KSR at 1740.

The Court also recognized that when the prior art taught away from the claimed invention, the invention was more likely to be non-obvious: "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1996).

The Court also emphasized the importance of identifying "a reason" that a person of ordinary skill in the relevant field would have combined the elements in the fashion claimed by the new invention. *Id.* at 1731. The Court also emphasized that this analysis should be made explicit:

> Often it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an

> apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

Id. at 1740-1741 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The present claims are directed to pharmaceutical compositions and solid oral dosage forms comprising the pharmaceutical compositions, wherein the compositions consist of a hydrophobic or macromolecular drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. The transitional phrase "consisting of" indicates that there are no unlisted components present in the pharmaceutical compositions.

In contrast, Watts *et al.* discloses unambiguously the use of a ***two-component*** absorption promoter as follows.

> The present invention therefore provides a drug delivery composition for colonic delivery comprising a polar drug, an absorption promoter which (a) comprises a mixture of a fatty acid having 6 to 16 carbon atoms or a salt thereof *and a dispersing agent* or (b) comprises a mixture of mono/diglycerides of medium chain fatty acids *and a dispersing agent* and means adapted to release the polar drug and absorption promoter in the colon.

Watt *et al.*, page 5, lines 10-16 (emphasis added). Both of the Watts *et al.* embodiments describe the absorption promoter as a two-component mixture in which one component ***must*** be a dispersing agent while the other may be either: (1) a medium chain fatty acid or salt; or (2) a mixture of mono/diglycerides of medium chain fatty acids. Clearly, the scope of the disclosure of Watts *et al.* extends ***only*** to the use of two-component absorption promoters. Example 3 in Watts *et al.*, presented to represent a formulation that is poorly absorbed, uses capric acid alone as the enhancer, and is used to establish the necessity of dispersing agent, which is a surfactant, a category of chemicals generally considered to have utility as absorption promoters. All of the embodiments which employ a medium chain fatty acid or salt thereof in the absorption promoter ***must also contain*** a dispersing agent as a second component of the absorption promoter. Watts *et al.* defines the term "dispersing agent" to include "an agent that is able to position itself at the interphase between the formulation phase

and the aqueous phase in the colon and thereby reduce the interfacial tension between the two phases and promote the dispersion of the formulation in the lumen of the colon." Watts *et al.*, page 5, line 30 to page 6, line 4.

Importantly, Watts discloses that:

> We have surprisingly found that polar drugs are advantageously delivered to the colon and that the absorption of polar drugs from the colon is greatly enhanced by administering the drug with a mixture of fatty acid having 6 to 16 carbon atoms or related mono/diglycerides and a pharmaceutically acceptable dispersing agent. It has surprisingly been found that the mixture of fatty acid or related mono/diglycerides and pharmaceutically acceptable dispersing agent gives a *synergistic effect* which is much greater than that obtained from each agent below.

Watts at page 5, lines 1-8 (emphasis added).

Thus, Watts leads one of ordinary skill in the art to combine mixture of fatty acids or mono/diglycerides and a dispersing agent in order to obtain a "synergistic effect." One of ordinary skill in the art who was aware of Watts certainly would not delete one of the components in Watts in an effort to improve the compositions recited therein. Thus, the present invention is not just a predicable variation of what was known the art. As a consequence, the Examiner has failed to make a *prima facie* case of obviousness.

The presently claimed pharmaceutical compositions do not have a two-component absorption enhancer and do not contain any type of dispersing agent as defined in Watts *et al.* Thus, Watts *et al.* does not disclose compositions consisting of each of the components as recited in the present claims. Moreover, Watts *et al.* does not provide any reason to produce compositions consisting of a drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list.

The Examiner alleges that Applicants' arguments are selectively focused towards only certain aspects of the teachings of Watt *et al.* and do not consider the art as a whole. (Office Action, page 4). The Examiner refers to the statement in Watts *et al.* that "[i]t has been known for some time that sodium caprate can act as an absorption promoting agent" and the

citation therein to Kajii *et al.* (J. Pharm. Sci. 77:390 (1988)) to state that it was quite clear that drugs have enhanced systemic absorption from compounds, specifically sodium caprate. (Office Action, page 4).

Applicants respectfully disagree with the characterization of the references. First, the statement in Watts *et al.* as to Kajii *et al.* is incorrect as Kajii *et al.* (attached hereto as Exhibit A) relates to studies on sodium caprylate, not sodium caprate. Second, the experiments carried out by Kajii *et al.* were *in vitro* experiments on the ability of sodium caprylate to enhance the penetration of fluorescent dyes through isolated brush border membrane vesicles. One of ordinary skill in the art would not recognize the *in vitro* results disclosed in Kajii *et al.* to be a teaching that sodium caprylate or any other medium chain fatty acid salt, by itself, is capable of enhancing intestinal absorption of drugs *in vivo*.

Moreover, Kajii *et al.* must be taken in the overall context of Watts which unmistakably directs one to combine a fatty acid or mono/diglyceride thereof with a dispersing agent in order to obtain improved, even synergistic, results. One who was aware of Watts would certainly not remove a component that was taught to lead to synergistic results.

The Examiner points to Figures 1-3 and 11 of Watts *et al.* to state that "it is quite clear that Watts teaches the enhancing effects of sodium caprate on active agents." (Office Action, page 4).

Applicants respectfully disagree and assert that the Examiner has mischaracterized the disclosure of Watts *et al.* None of the experiments shown in Figures 1-3 and 11 involve the use of sodium caprate. Figure 1 shows the results of a comparison between insulin alone and an insulin/Labrasol/capric acid formulation. Figure 2 shows the effect of an insulin/Labrasol formulation without any fatty acid. Figure 3 shows the effect of an insulin/capric acid formulation. Figure 11 shows the results of a comparison between calcitonin alone and a calcitonin/Labrasol/capric acid formulation. Thus, these experiments do not disclose the use of sodium caprate.

The Examiner specifically points to Figure 3 as teaching the enhancing effects of sodium caprate as a single enhancer. (Office Action, page 4). The Examiner further states

that "Watts clearly shows that an oral dosage form comprising insulin has a much increased bioavailability in the presence of the caprate anion in the [gastrointestinal tract]". (Office Action, page 6).

Applicants respectfully disagree. First, the experimental results shown in Figure 3 do not involve sodium caprate. Second, the data shown for the effect of the insulin/capric acid formulation cannot be interpreted as the results are not compared to the effect of insulin alone. One cannot determine if the capric acid had any enhancing effect at all based on this disclosure. Third, any data showing that capric acid enhances the absorption of insulin occurs only in the presence of a dispersing agent (Labrasol), so the effect of capric acid alone is undisclosed. In fact, as noted above, the example using capric acid alone appears to be the example Watts *et al.* uses to represent a system with no enhancement present.

The Declaration of Thomas W. Leonard, Ph.D. Pursuant to 37 C.F.R. § 1.132 ("the Leonard Declaration"), attached hereto, describes experiments testing the ability of capric acid to enhance delivery of a polar drug (paragraphs 19 and 20). Capsules were prepared containing alendronate alone or alendronate with either capric acid or sodium caprate and orally administered to dogs. The excretion of alendronate was than determined as a measure of intestinal absorption of alendronate. The experiments showed that capric acid did not enhance the intestinal absorption of alendronate over the absorption of alendronate alone (see Table 4). In contrast, the experiments presented in the Declaration show that the alendronate/sodium caprate formulation resulted in a doubling of the amount of alendronate absorbed. It is clear from these results that sodium caprate is very active as an absorption enhancer, however, capric acid has no activity at all unless formulated in the two component systems specified in Watts *et al.* Thus, capric acid and sodium caprate are *not* interchangeable in a pharmaceutical formulation in the absence of a dispersing agent.

The Examiner notes that the present claims use closed language to describe the pharmaceutical formulation, but states that part (C) of the claims adds considerable breadth reading on most excipients.

Applicants respectfully disagree. The Examiner has not cited any evidence that any of the excipients of Part (C) of claim 258 and other independent claims includes any of the

dispersing agents of Watts. Part (C) lists a defined set of excipient categories. It is clear that the listed excipient categories do not encompass the dispersing agent of Watts *et al.* as the definition of dispersing agent in Watts *et al.* ("an agent that is able to position itself at the interphase between the formulation phase and the aqueous phase in the colon and thereby reduce the interfacial tension between the two phases and promote the dispersion of the formulation in the lumen of the colon") does not fall within any of the listed excipient categories. Thus, the breadth of part (C) does not render the claims obvious over Watts *et al.*, alone or in combination with other references.

The Examiner alleges that the formulations taught by Watts *et al.* are solid at room temperature, pointing to Example 10 on page 22. (Office Action, page 5).

Applicants respectfully disagree. Watts *et al.* teaches that the disclosed formulations are liquids or semi-solids (page 8, line 21). Watts *et al.* further discloses that a 50:50 mixture of dispersing agent and capric acid will be a semi-solid at room temperature (page 8, lines 21-25). As the formulation described in Example 10 of Watts *et al.* is a 50:50 mixture of dispersing agent (Labrasol) and capric acid, it is clearly not a solid at room temperature.

The Examiner alleges that Watts *et al.* teaches the use of a single enhancer with insulin and capric acid in Figure 3 and that the absorption promoter can be used alone.

Applicants respectfully disagree. As previously noted, Watts *et al.* discloses a composition of sodium insulin and capric acid in a comparative example (Example 3) in order to demonstrate the inferior effect of capric acid as the only enhancer compared to the synergistic effect realized by their two component absorption promoter. Moreover, because there was no insulin-only control used in Example 3, the example provides no evidence that the insulin/capric acid formulation provides any more delivery of insulin to the intestine than a formulation of insulin alone. Thus, one of ordinary skill in the art reading Example 3 would not consider it to teach the use of a single enhancer to deliver drugs to the intestine. While Watts *et al.* discloses sodium caprate as a fatty acid salt that can be used in the multi-component formulations, Applicants strongly disagree with the Examiner's contention that Watts *et al.* teaches the use of sodium caprate alone. The Examiner has not pointed to any location in Watts *et al.* that has this teaching. The Examiner again cites the statement in

Watts *et al.* that "[i]t has been known for some time that sodium caprate can act as an absorption promoting agent" based on the *in vitro* cell data of Kajii *et al.*, but this is clearly not a teaching that a formulation comprising sodium caprate as the only absorption enhancer will be effective to deliver a drug and the enhancer to the intestine.

The Leonard Declaration describes experiments comparing the ability of capric acid and sodium caprate to function in solid dosage forms. The results show that capric acid, either alone or combined with an excipient to enhance the pharmaceutical properties (sorbitol), is incapable of flowing from a machine hopper into a tablet die or capsule shell body for production of a solid dosage form (paragraphs 4-5). The capric acid or capric acid/sorbitol mixture could not be passed through a screen to improve the flow characteristics because even minimal handling of capric acid (which has a melting point of 31°C) leads to melting and clogging of the screens (paragraph 6). Even attempts to prepare tablets containing capric acid by hand were unsuccessful as quantifiable amounts of capric acid were stuck on the table die due to its melting (paragraph 7). The low melting point and other physical characteristics of capric acid were well known to those of ordinary skill in the art. Thus, any teaching of Watts *et al.* that capric acid could be used alone to produce a solid dosage form or to enhance absorption is incorrect. In contrast, sodium caprate exhibited good flow characteristics and was readily compressed into tablets, showing that capric acid and sodium caprate are not interchangeable in terms of solid dosage forms.

The Leonard Declaration further describes efforts to produce tablets of capric acid and Labrasol as disclosed in Example 3 of Watts *et al.* These efforts failed as Labrasol, which is a liquid, squirted out of the tablet die during compression (paragraph 8). These results show that the compositions of Watts *et al.* are not useful for making tablets.

The Leonard Declaration also describes tablet disintegration experiments comparing capric acid and sodium caprate (paragraph 9). While sodium caprate tablets were found to exhibit rapid disintegration times, the capric acid tablets did not disintegrate at all at 25°C and simply melted and remained on top of the bath water at 37°C (Table 2). These results demonstrate the unsuitability of capric acid in solid oral dosage forms.

Additional experiments described in the Leonard Declaration involved preparation of insulin formulations with medium chain fatty acids or fatty acid salts with and without Labrasol as described in Watts *et al.* (paragraphs 10-18). The formulations were placed in capsules and dissolution of each formulation was measured. For the capric acid formulations, there was little dissolution of the insulin in the absence of Labrasol, and the amount of dissolution was greatly increased in the presence of Labrasol. Thus, the presence of capric acid in the formulation had little or no effect on the dissolution of the insulin. The lack of effect of capric acid was confirmed in animal studies with alendronate/capric acid formulations as described above and in paragraphs 19 and 20 of the Leonard Declaration. In contrast, the insulin/sodium caprate formulations dissolved completely in the absence of Labrasol. In fact, the presence of Labrasol actually depressed the dissolution of insulin in the formulations comprising insulin and sodium caprate or fatty acid salts with longer chain lengths. As only insulin that is dissolved in the GI tract contents can be absorbed, these data demonstrate that a sodium caprate/Labrasol /insulin formulation will have less drug absorbed than a sodium caprate/insulin formulation. This is clearly a result that is opposite to the teachings of Watts *et al.*

The disclosure in Example 3 of Watts *et al.* of a formulation containing insulin and capric acid as the only absorption enhancer was uninformative regarding enhancement of absorption and provides no reason why one of ordinary skill in the art would prepare the presently claimed solid oral dosage forms. The experimental results disclosed in the Leonard Declaration show that any teaching from Watts *et al.* regarding the use of capric acid alone was incorrect as capric acid is wholly unsuitable for use in tableting formulations. Further, the Leonard Declaration makes clear that capric acid and sodium caprate do not have similar physical properties and are not interchangeable. Thus, one of ordinary skill in the art reading Watts *et al.* would not have any reason to use sodium caprate or other medium chain fatty acid salts as the only absorption enhancer in a solid oral dosage form as is presently claimed.

The Examiner alleges that sodium caprate and capric acid prepared in a formulation similar to Example 3 of Watts *et al.* would result in all components being a solid at room temperature. (Office Action, page 6).

Applicants respectfully disagree. As discussed above, Watts *et al.* clearly indicates that the insulin/capric acid formulation of Example 3 is a semi-solid, not a solid.

The Examiner is of the opinion that it would have been obvious to one of ordinary skill in the art to combine the teachings of Watts *et al.* and Heiber *et al.* because Watts *et al.* teaches tablet dosage forms and Heiber *et al.* teaches that certain formulations can be pressed into tablet form from a dry blend of a drug (low molecular weight heparin) and an enhancer.

Applicants respectfully disagree. Watts *et al.* fails to teach formulations comprising sodium caprate or any other fatty acid salt as the only absorption enhancer. Heiber *et al.* does not remedy the deficiencies in Watts *et al.* Heiber *et al.* discloses compositions for administering a drug to the oral mucosa. The compositions comprise a macromolecular drug, a bile salt or bile salt analog, and a hydrophilic polymer. Heiber *et al.*, column 5, lines 14-24. Heiber *et al.* does not disclose any compositions consisting of a drug and a salt of a medium chain fatty acid as the only absorption enhancer. Moreover, Heiber *et al.*, taken either alone or in view of Watts *et al.*, does not provide any reason to produce such a composition.

The Examiner states that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention because Watts *et al.* clearly shows that an oral dosage form comprising insulin has a much increased bioavailability in the presence of the caprate anion in the [gastrointestinal tract]." (Office Action, page 6).

Applicants strongly disagree with the Examiner's statement as Watts *et al.* provides no teaching whatsoever that formulations comprising sodium caprate or capric acid as the only absorption enhancer increases the bioavailability of insulin or any other drug.

The Examiner alleges that the differences between the claimed formulations and what is taught by Watts *et al.* and Heiber *et al.* is considered well-known in the art and/or routine, citing Teng *et al.*, Garces *et al.*, and Bachynsky *et al.* (Office Action, page 7).

Applicants respectfully disagree. Teng *et al.* does not remedy the deficiencies in Watts *et al.* and Heiber *et al.* Teng *et al.* relates to pharmaceutical compositions for delivery of oligonucleotides. The compositions comprise various absorption enhancers selected from the classes of surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Teng *et al.*, column 7, lines 44-50. Teng *et al.* does not disclose any

compositions comprising a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms as the only absorption enhancer. The Examiner points to Example 15 of Teng *et al.*, but this example discloses formulations comprising three absorption enhancers: sodium chenodeoxycholic acid, sodium laurate, and sodium caprate. Teng *et al.* taken either alone or in view of the other cited references, does not provide any reason to produce a formulation comprising a medium chain fatty aid salt as the only absorption enhancer.

Garces *et al.* does not remedy the deficiencies in Watts *et al.* and Heiber *et al.* Garces *et al.* relates to pharmaceutical compositions comprising millispheres made up of drugs mixed with gellable hydrocolloids and coated with cationic polysaccharides. Garces *et al.*, column 2, lines 10-27. Garces *et al.* does not disclose any compositions consisting of a drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. None of the formulation techniques in Garces *et al.* will allow formation of a solid dosage form from the two component systems used in the examples in Watts *et al.* Garces *et al.* taken either alone or in view of the other cited references, does not provide any reason to produce such a composition.

Bachynsky *et al.* does not remedy the deficiencies in Watts *et al.* and Heiber *et al.* Bachynsky *et al.* relates to pharmaceutical compositions comprising an antibacterial compound and a two-component absorption–enhancing system made up of (1) an ether of a C_6 to C_{18} alcohol and a polyoxyethylene glycol and a second component selected from among (2)(i) a polyoxyethylene glycol C_6 to C_{18} carboxylic acid glyceride ester, (2)(ii) a C_6 to C_{18} carboxylic acid or pharmaceutically acceptable salt thereof and (2)(iii) an ester of two or more C_6 to C_{18} carboxylic acids, glycerol and a polyoxyethylene glycol. Bachynsky *et al.*, column 2, lines 3-19. Bachynsky *et al.* does not disclose any compositions consisting of a drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. Bachynsky *et al.* taken either alone or in view of the other cited references, does not provide any reason to produce such a composition.

Thus, none of the cited references, either alone or together, provide a reason why one of ordinary skill in the art would prepare a pharmaceutical composition ***consisting of*** a hydrophobic or macromolecular drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. In fact, Watts directs one to add a dispersing agent to obtain synergistic results, thus teaching away from the claimed invention. In addition, none of the cited references provide any reason to modify the compositions disclosed therein to contain a medium chain fatty acid salt in particulate form as the only absorption enhancer, and none of the cited references provide a reasonable expectation that a composition containing a medium chain fatty acid salt in particulate form as the only absorption enhancer would successfully deliver a drug to the intestine.

It is respectfully requested that the rejection of claims 258-264, 266, 268, 275, 276, 278, 279, 283-286, 289, 292, 295, 296, 302, 303, 306, 309, 310, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344, and 345 be withdrawn.

(B) Claims 258-264, 266, 268, 275, 276, 278, 279, 283-286, 289, 292, 295-300, 302, 303, 306, 309, 310-314, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344, and 345 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Watts *et al.* (International Application No. WO 97/05903) in view of Heiber *et al.* (U.S. Patent No. 5,346,701), and optionally any one or more of Teng *et al.* (U.S. Patent No. 6,747,014), Garces *et al.* (U.S. Patent No. 5,736,161), and Bachynsky *et al.* (U.S. Patent No. 5,190,748), and further in view of Bürk *et al.* (U.S. Patent No. 5,221,734). (Office Action, pages 7-8). Applicants respectfully traverse this rejection.

The Examiner alleges that the teachings of the references cited in the previous rejection are incorporated herein and that Bürk *et al.* teaches formulations comprising the lubricant stearic acid and the disintegrant crospovidone. (Office Action, page 8).

Applicants respectfully disagree. As discussed above, Watts *et al.* and Heiber *et al.* are inadequate to establish a *prima facie* case of obviousness as neither reference provides a reason to prepare dosage forms containing medium chain fatty acid salts as the only absorption enhancer and fail to provide a reasonable expectation that such formulations

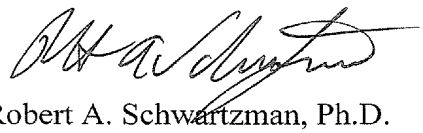
would be effective to deliver a drug and an enhancer to the intestine. Bürk *et al.* fails to remedy these deficiencies. Bürk *et al.* relates to pharmaceutical compositions comprising the polypeptide milk growth factor and provides a laundry list of possible pharmaceutical excipients (columns 11-12). Bürk *et al.* is silent regarding fatty acid salts or sodium caprate and their use as the sole absorption enhancer. Bürk *et al.* taken either alone or in view of the other cited references, does not provide any reason to produce such a composition. Thus, the Examiner has failed to make a *prima facie* case of obviousness.

It is respectfully requested that the rejection of claims 258-264, 266, 268, 275, 276, 278, 279, 283-286, 289, 292, 295-300, 302, 303, 306, 309, 310-314, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344, and 345 be withdrawn.

CONCLUSION

Accordingly, Applicants submit that the present application is in condition for allowance and the same is earnestly solicited. Should the Examiner have any small matters outstanding of resolution, he is encouraged to telephone the undersigned at 919-854-1400 for expeditious handling.

Respectfully submitted,



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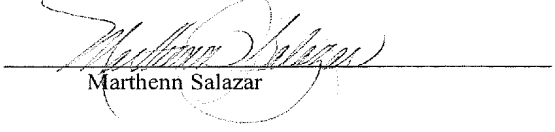
Signature: 
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